### Take-home messages in Hematology

**Intensive Review in Internal Medicine**  
July 16, 2012  
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BWH Hematology Division

**Nothing to disclose**

### Anemia

#### Morphological Classification of Anemias

<table>
<thead>
<tr>
<th>Microcytic</th>
<th>Normocytic</th>
<th>Macrocytic</th>
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<tbody>
<tr>
<td>MCV &lt; 80</td>
<td>MCV 80-95</td>
<td>MCV &gt; 95</td>
</tr>
</tbody>
</table>

- Iron deficiency  
- Anemia of chronic dx  
- Thalassemias  
- Sideroblastic anemia

- Renal failure  
- Anemia of chronic dx  
- Hypothyroidism  
- Blood loss  
- Aplastic anemia  
- Hemolysis

- Vit B12 def  
- Folate def  
- Hypothyroidism  
- Myelodysplasia  
- Alcohol liver Dx  
- Blood loss

### Evaluation of Anemia

- **Low retic index**  
  - Low MCV
  - Iron deficiency  
  - Anemia of chronic dx  
  - Thalassemias  
  - Renal failure  
  - Aplastic anemia  
  - Hypothyroidism  
  - B12/folate deficiency  
  - MDS  
  - Alcohol liver disease

- **Normal MCV**  
  - Hypothyroidism  
  - EPO deficiency  
  - Aplastic anemia  
  - MDS  
  - Alcohol liver disease

- **High MCV**  
  - Hemolytic anemia  
  - Blood loss

### Anemia of Chronic Inflammation

- Contributed to by - iron trapping in macrophages  
- ↓ iron absorption from GI tract

- IL-6 induction of **Hepcidin** is central to etiology
Topics in Anemia

**Diagnosis and Treatment of Iron Deficiency**
- Differentiating Fe Deficiency – High TIBC, low ferritin
- Soluble transferrin receptor – normal in ACI
- Bone marrow iron – normal in ACI

**Differentiating folate vs B12 deficiency**
- ↑ Methylmalonic acid & neurological deficits in B12 def.
- Intrinsic factor Ab - ~99% specificity for pernicious anemia

**Bone marrow iron**
- normal in ACI

**Soluble transferrin receptor**
- normal in ACI

**Hemolytic Anemias & Hemoglobinopathies**
- Hemolytic anemias - ↑LDH, ↑ retic count
- Spherocytes – AIHA or hereditary spherocytosis
- Schistocytes – microangiopathic hemolytic anemia
- Indications for exchange blood transfusion in SCD
- Stroke or Acute chest syndrome
- Diagnosis and Treatment of PNH
  Treatment: with monoclonal Ab Eculizumab

**Autoimmune Hemolytic Anemia**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Warm AIHA</th>
<th>Cold AIHA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direct Coombs</td>
<td>IgG or IgG &amp; C3</td>
<td>C3 only</td>
</tr>
<tr>
<td>Antibody</td>
<td>IgG</td>
<td>IgM</td>
</tr>
<tr>
<td>Eculizumab</td>
<td>Methylxop, Penicillin, Procainamide; leukemia, lymphoma</td>
<td>Quinidine, Paroxys. cold hemoglobinuria, lymphoma, Mycoplasma</td>
</tr>
<tr>
<td>Treatment</td>
<td>Steroids, Rituxan, splenectomy</td>
<td>No role for steroids Warm pt, Cytoxan</td>
</tr>
</tbody>
</table>

**Paroxysmal Nocturnal Hemoglobinuria**
- Acquired mutations of PIG-A gene → loss of glycosylphosphatidylinositol (GPI) anchor on RBCs, WBC & platelets
- GPI-anchored proteins include:
  - Membrane inhib of reactive lysis (MIRF, CD59)
  - Decay Accelerating Factor (DAF, CD55)
- MIRF & DAF protect against c⁻mediated lysis
- Resultant unrestricted c⁻mediated lysis of RBCs

**Megaloblastic Anemia**
- Caused by Vitamin B₁₂ or Folate deficiency
- Hypoproliferative – low retic index
- Macro-ovalocytes
- hypersegmented neutrophils (>5 lobes)
- Intrinsic factor (IF) Abs – Pernicious anemia
- Drugs – methotrexate, pentamidine, dilantin, triamterene, pyrimethamine

**Eculizumab**
- Recombinant humanized monoclonal Ab binds to complement protein C5 inhibiting its cleavage into C5a and C5b, which prevents the generation of the terminal complement complex C5b-9.
- Inhibits formation of Membrane Attack Complex responsible for intravascular hemolysis in PNH.
Treatment of Sickle Cell Disease

Rx of Bone pain crisis – Fluid repletion and liberal pain medication as needed

Rx to prevent frequent crises – Hydroxyurea

Indications for Exchange Blood Transfusion
- Impending Acute Chest Syndrome
- Stroke-in-evolution/TIA
- Severe unrelenting bone pain crisis with end organ deterioration

α-thalassemia (Quantitative Defect)

- Absent or ↓ production of α chains of hemoglobin

<table>
<thead>
<tr>
<th>Locus Defect</th>
<th>Nomenclature</th>
<th>Clinical manifestation</th>
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</thead>
<tbody>
<tr>
<td>αα/α−</td>
<td>α-thal trait</td>
<td>asymptomatic</td>
</tr>
<tr>
<td>α−/α− or αα/−</td>
<td>α-thal minor</td>
<td>little to no anemia</td>
</tr>
<tr>
<td>α−/−</td>
<td>α-thal HbH</td>
<td>moderate hemolysis, transfusions in adulthood</td>
</tr>
<tr>
<td>−/−</td>
<td>α-hydrops fetalis</td>
<td>death in utero</td>
</tr>
</tbody>
</table>

β-thalassemia (Quantitative Defect)

- ↓ or absent production of β chains of hemoglobin
- Have low MCV and ↑HbA2

<table>
<thead>
<tr>
<th>Clinical Nomenclature</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>β- thal major (Cdiey’s Anemia)</td>
<td>severe anemia, ↑↑↑HbF, ‘chipmunk facies’ transfusion dependent for life.</td>
</tr>
<tr>
<td>β- thal intermedia</td>
<td>mod. anemia, non-transfusion dependent</td>
</tr>
<tr>
<td>β- thal minor</td>
<td>mild or no anemia, ↑RBC count</td>
</tr>
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</table>

β-thalassemia (Quantitative Defect)

- Due to abnormality of the integral proteins underlying the RBC membrane
- Loss of RBC membrane in the spleen → spherocytes
- Chronic premature hemolysis → early gall stones
- >65% are autosomal dominant – (+) family hx
- MCHC ≥ 39

Diagnosis : Increased osmotic fragility

Treatment : Folic acid, Splenectomy - limits hemolysis

Hereditary Spherocytosis

- Due to abnormality of the integral proteins underlying the RBC membrane
- Loss of RBC membrane in the spleen → spherocytes
- Chronic premature hemolysis → early gall stones
- >65% are autosomal dominant – (+) family hx
- MCHC ≥ 39

Diagnosis : Increased osmotic fragility

Treatment : Folic acid, Splenectomy - limits hemolysis

Risk Factors for VTE

<table>
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<tr>
<th>Transient/Provoked</th>
<th>Persistent</th>
<th>Idiopathic/Unprovoked</th>
</tr>
</thead>
</table>
| Surgery            | Obesity    | ????
| Trauma (major trauma or lower-extremity injury) | Chronic Medical Illnesses | High FVIII, Acquired APCR |
| Acute medical illness | Cancer and its therapy | High FIX, XI |
| Immobilization     | Inflammatory bowel disease | |
| Estrogen-containing contraceptives or hormone replacement therapy | Nephrotic syndrome | |
| Pregnancy/puerperium | Myeloproliferative neoplasms/PNH | |
| HIT                 | Paralysis   | |
| Prolonged air travel (operationally manage as idiopathic) | | |
**VTE Risk Factor Model**

- **Intrinsic Thrombosis Risk**
  - Genes
    - Anticoagulant deficiencies
      - Antithrombin 20-fold
      - Protein S 10-fold
      - Protein C 10-fold
      - Prothrombin 3-fold
      - Factor V Leiden 3-8 fold
    - Triggering Factors
      - Estrogens
      - Pregnancy
      - Surgery
      - Immobilization
      - Inflammation
- **Acquired Risk Factors**
  - Age
  - Previous VTE
  - Cancer
  - Obesity
  - LAC

**Prophylaxis**

**Thrombosis Threshold**

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**Clinical Clues for Thrombophilias**

- Age of onset <50
- Recurrent thrombosis
- Positive family history in 1st degree relative
- Unusual location/site

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**Who to Test?**

- **Yes**
  - VTE at age <50 with positive family history (1st degree relatives)
  - Cerebral venous thrombosis
  - Portal/mesenteric vein thrombosis (r/o MPD, PNH)
  - Pregnancy loss (2nd and 3rd trimester)
- **Reasonable**
  - VTE in association with OCPs/HRT or pregnancy
- **No**
  - Patients > 50 with first spontaneous VTE
  - VTE in patients with active cancer
  - Elderly patients with postoperative VTE
  - Retinal vein thrombosis
  - Arterial thrombosis (except paradoxical emboli)
  - Asymptomatic patients with no personal or familial hx of VTE
  - Women going on OCPs with no familial hx of VTE

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**APS**

- True antiphospholipid syndrome has high risk of recurrence.
  - Updated Sapporo criteria 2006
- Long term anticoagulation in the setting of 1st unprovoked VTE event and persistently positive LA test results is required.
- Warfarin target range 2.0-3.0 sufficient

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**Duration of Anticoagulation**

- **Provoked**
  - 3 months sufficient if risk gone
  - 1% risk per year of recurrence, not changed by 3 vs 6 months
- **Idiopathic**
  - Recurrence rate highest in first 2 years
    - 10% per year in 1st 2 years
    - 40% at 5 years

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**Unprovoked VTE**

- Recent ISTH consensus considers an annual risk of VTE recurrence below 5% as acceptable to deny life-long anticoagulant therapy. (Kearon et al. JTH 2010)

**How to determine risk?**

- **D-dimer**
  - Elevated level associated with increased recurrence
  - Measure at end of initial duration and one month after d/c

- **Residual vein thrombosis**
  - Persistent clot associated with increased recurrence
  - Continue anticoagulation until resolution

- **Clinical prediction scores**
  - Vienna nomogram, DASH score, others
### DASH Score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Description</th>
<th>Score</th>
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</thead>
<tbody>
<tr>
<td>D</td>
<td>D-dimer</td>
<td>+2</td>
</tr>
<tr>
<td>A</td>
<td>Age &lt; 50 years</td>
<td>+1</td>
</tr>
<tr>
<td>S</td>
<td>Male Sex</td>
<td>+1</td>
</tr>
<tr>
<td>H</td>
<td>Hormone use at time of VTE</td>
<td>-2</td>
</tr>
</tbody>
</table>

In males, the score may range from 1 to 4
In females, the score may range from -2 to 3

### Annualized recurrence rates

**Requires prospective validation in large population**

### Summary

- The “hypercoaguable state” has a wide spectrum and reflects an accumulation of additive risk factors.
- Duration of anticoagulation depends on the risk of recurrent VTE.
  - Treatment of provoked VTE straightforward—short-term anticoagulation with minimal risk of recurrence.
  - Improved risk stratification will aid in determining duration of anticoagulation therapy for unprovoked VTE.
  - “Personalized” risk profiles and patient preference increasingly considered.
  - Alternatives to full intensity anticoagulation, such as ASA, or other non-anticoagulant based risk modification strategies may be identified in the future.

### Oral Anticoagulants

- **-xaban** direct Xa inhibitor
- **-gatran** direct thrombin inhibitor
- **-paranux** indirect Xa inhibitor

### Novel Oral Anticoagulants

- **Direct Factor Xa Inhibitors**
  - Apixaban
  - Edoxaban
  - Betrixaban

- **Direct Thrombin (IIa) Inhibitors**
  - Hirudin
  - Argatroban
  - Edesina
**Novel Oral Anticoagulants**

- **Dabigatran**: PRADAXA
  - FDA approved for afib Oct 2010
  - EMA: post ortho VTE ppx March 2008
    - Afib Aug 2011
- **Rivaroxaban**: XARELTO
  - FDA approved for post ortho VTE July 2011
  - FDA approved for afib Nov 2011
  - Canada and EMA > 3 years post ortho VTE ppx
  - EMA: afib and DVT treatment Dec 2011
- **Apixaban**: ELIQUIS
  - EMA approved post orth VTE prophylaxis May 2011

**Antidote: PCC Results**

- **Rivaroxaban**
  - PCC completely reversed INR back to baseline ($p < 0.001$)
  - PCC completely normalized endogenous thrombin potential ($p < 0.001$)
- **Dabigatran**
  - PCC did not correct elevated PTT
  - PCC did not correct elevated TT
  - PCC did not correct elevated ECT

**Novel Oral Anticoagulants summary**

**Novel oral anticoagulants offer:**
- Similar or improved efficacy and safety
  - Decreased ICH for AF but increased GI bleeds
- Pharmacologic advantages
- Ease of administration
- Outpatient management of DVT/PE without need for parenteral agents
- Intriguing possible uses
  - ACS
  - HIT

**Bleeding Disorders**

**Bleeding Presentations**

- Primary: vWF and pltS
  - Skin
  - Petechiae
  - Ecchymoses
  - Small cuts, shaving
  - Mucosal surfaces
  - Epistaxis
  - Immediately after trauma or surgery
  - Tonsils
  - Teeth
  - menorrhagia
  - medications

- Secondary: coag factors
  - Joints
  - Hemarthrosis
  - Deep soft tissue
  - Deep muscle hematomas
  - Large skin ecchymoses
  - Delayed after surgery
    - Circumcision
    - Deep hematoma disproportionate to degree of trauma
    - Initial hemostasis, bleeding hours after procedure

**Assessment of hemostasis**

- Patient history
  - Congenital vs acquired?
- Patient reporting of bleeding events very subjective
  - Location, duration and number of bleeds
  - Transfusions
  - Menstruation/childbirth
  - Packing, stitching, back to OR
  - Medications
- Family history
  - X-linked: hemophilia,
  - autosomal dominant: vWD
- Laboratory tests
Platelet Aggregation Studies

Platelet-rich plasma from patient

Epinephrine
ADP
Collagen
Arachidonate
Ristocetin (RIPA)

Platelet Function Studies

<table>
<thead>
<tr>
<th>Epineph</th>
<th>Collagen</th>
<th>ADP</th>
<th>Arach</th>
<th>Ristocet</th>
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<tbody>
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<td>Second</td>
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<td>decreased</td>
<td>wave</td>
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<tr>
<td>absent</td>
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Disorder

- vWD
- Glanzmann's thrombasthenia
- Thrombocytopenia
- Storage pool disorders
- Signaling disorders
- Mutations: MPL, MHY19, WAS, RUNX1

Platelet Disorders

INHERITED
- Bernard-Soulier—gpl1b/IX/V
- Glanzmann’s thrombasthenia—gpl1b/llla
- Storage pool disorders
- Signaling disorders
- Mutations: MPL, MHY19, WAS, RUNX1

AQUIRED
- Normal platelet count
  - Drugs, uremia, myeloproliferative disorders, myelodysplastic syndrome, paraproteins
- Thrombocytopenia
  - ITP, collagen vascular disease, lupus anticoagulant, quinina/drugs, marrow suppression, splenic sequestration

Thrombocytopenia

- Immune Thrombocytopenia Purpura
- Thrombotic Thrombocytopenia Purpura
- DIC
- Drug Effect
- Primary Bone Marrow Disorder
- Pseudo-thrombocytopenia

Heparin-Induced Thrombocytopenia

- > 50% fall in platelet count
- Usually 4 days after start of heparin
- Venous thromboembolism
- Re-exposure can occur after 1 day of heparin
- 90% of suspected cases are something else

Pathogenesis of HIT

- Heparin-PF-4 antibody complex
- Only complexes with IgG are pathogenic
- Bind to platelet Fc gamma IIa receptor and cause platelet activation
- Immunogenicity UFH >> Low Mr heparin >> fondaparinux
- 15% --- <1% --- ? (several cases)
Fibrin stabilizes platelet plug

Coagulation Cascade Screening Tests

aPTT  PT  TT

Coagulation Factor Deficiencies

**INHERITED**
- Hemophilia A or B most common
- Factor XI, Factor VII, Factor XIII*
- All the rest

**ACQUIRED**
- Inhibitors
  - Usually to FVIII, rarely vWF, other factors
- Drugs
- Liver disease
- Paraproteins
- Tumors, vascular anomalies

Hemophilia Treatment

FVIII and FIX Treatment
- Minor procedures or bleed (Scrapes, cuts, bruising)
  - 30-50% for 1-2 days
- Moderate (Dental procedures, epistaxis, hematuria)
  - 50% for 2-7 days
- Major (CNS, major joint bleeds, major surgery)
  - 80-100% for first day, 60-100% for 7-10 days

Products for Treatment
- Recombinant products preferred
- Plasma derived products all undergo viral inactivation
  - Intermediate purity—contain vWF
  - High purity
- Plasma or cryo—avoid unless no alternative

Factor XI Deficiency

- Autosomal Transmission
- Higher prevalence in Ashkenazi population which may approach 1:1000
- Levels do not necessarily correlate with bleeding (patients may bleed with levels above 30%)
- Patients may present late in life with no prior bleeding history

Factor VIII Inhibitors

- Congenital Hemophilia
  - develop in about 5 to 10% of children early in the course of treatment
  - low titer versus high titer responders
- Acquired Hemophilia
  - idiopathic, associated with malignancy, rheumatologic disease and pregnancy
  - soft tissue bleeding predominates
**vWD Classification**

**Type I**: autosomal dominant, **quantitative** decrease in vWF and **concordant** decrease in all functions

70-80% of vWD cases

**Type III**: homozygous recessive, almost no detectable vWF

Very Rare

**Type II**: Qualitative Abnormalities

A: decreased large mw multimers

10-15% of VWD

B: gain of function mutations, increased binding to gpIb

M: loss of function mutations, decreased gp1b binding

N: loss of function mutations, decreased FVIII binding

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**When to Use What**

- **Desmopressin (ddAVP)**
  - Mild Type I disease for most procedures
  - Moderate Type I disease for minor procedures
  - Mild Type IIA disease for minor procedures
  - Intermediate purity factor concentrates
  - Moderate/severe Type I disease for major procedures
  - All other procedures in Type IIA patients
  - All significant procedures in Type IIB patients

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**vWD Treatment**

- **DDAVP**
  - Release stored vWF from Weibel-Palade bodies
  - Onset of action within 30 mins
  - Tachyphylaxis

vWF containing concentrates: plasma derived pathogen-inactivated. Dose by FVIII or vWF.

- Humate-P
- Alphanate

- **Cryo**
  - Only as last resort

- **Recombinant vWF**
  - Clinical trials